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Oral administration of famciclovir for treatment of spontaneous ocular, respiratory, or dermatologic disease attributed to feline herpesvirus type 1: 59 cases (2006–2013)

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OBJECTIVE
To evaluate outcomes for cats treated with orally administered famciclovir 3 times/d for clinical signs attributed to naturally occurring feline herpesvirus type 1 (FHV-1) infection and to assess variables related to owner satisfaction with the treatment.

DESIGN
Retrospective case series.

ANIMALS
59 client-owned cats.

PROCEDURES
Medical records were reviewed to identify cats treated for presumed FHV-1 infection from 2006 through 2013 with ≥ 1 follow-up visit. Signalment, duration of clinical signs, prior treatment, examination findings, diagnostic test results, concurrent treatments, and outcome data were recorded. Owners were asked to complete a survey regarding patient- and treatment-related variables. Data were compared between cats that received low (approx 40 mg/kg [18 mg/lb]) and high (approx 90 mg/kg [41 mg/lb]) doses of famciclovir, PO, 3 times/d.

RESULTS
Patient age ranged from 0.03 to 16 years. Conjunctivitis (51/59 [86%]), keratitis (51 [86%]), blepharitis (19 [32%]), nasal discharge or sneezing (10 [17%]), and dermatitis (4 [7%]) were common findings. Clinical improvement was subjectively graded as marked in 30 (51%) cats, mild in 20 (34%), and nonapparent in 9 (15%). Median time to improvement was significantly shorter, and degree of improvement was significantly greater in the high-dose group than in the low-dose group. Adverse effects potentially attributable to famciclovir administration were reported for 10 cats. On the basis of survey responses, most (29/32 [91%]) owners were satisfied with their cat's treatment.

CONCLUSIONS AND CLINICAL RELEVANCE
Famciclovir at the prescribed dosages was associated with improved clinical signs in cats with presumed FHV-1 infection, and few adverse effects were attributed to the treatment. Further studies are needed to assess whether a famciclovir dosage of 90 versus 40 mg/kg, PO, 3 times/d would result in increased efficacy and shorter treatment time. (*J Am Vet Med Assoc* 2016;249:526–538)

Famciclovir, an oral prodrug of penciclovir, is an increasingly common treatment for FHV-1–infected cats.[1,2] Penciclovir is a nucleoside deoxyguanosine analog with potent antiviral activity against HSV-1, HSV-2, and varicella zoster virus,[3] as well as variable in vitro activity against FHV-1.[4–8] Penciclovir is consistently more potent than acyclovir, the only other drug used for the systemic treatment of cats infected with FHV-1.[4,5,7,9,10] Penciclovir has low bioavailability in humans, and an oral prodrug, famciclovir, is used instead. In cats, the pharmacokinetics of penciclovir following oral famciclovir administration is complex and nonlinear and differs markedly in comparison to other species studied.[11–13] For example, bioavailability of penciclovir in cats is only 7% following a single oral dose of 90 mg of famciclovir/kg (41 mg/lb),[13] whereas in people, the bioavailability is 77% after oral administration of approximately 7 mg of famciclovir/kg (3.2 mg/lb).[14] Results of a study[13] in cats showed that 1 oral dose of 40 or 90 mg of famciclovir/kg (18 or 41 mg/lb) resulted in similar maximum observed plasma concen-

ABBREVIATIONS

FHV-1	Feline herpesvirus type 1
HSV	Herpes simplex virus
USG	Urine specific gravity

trations and areas under the plasma concentration-time curve for penciclovir. Furthermore, penciclovir is present in the tears of cats at potentially therapeutic concentrations following oral administration of approximately 40 mg of famciclovir/kg 3 times/d.[15]

A limited number of studies[12,16] evaluating the efficacy of famciclovir in cats have been published in the literature. In 1 study,[12] famciclovir (90 mg/kg, PO) was administered 3 times/d (8:00 AM, 2:00 PM, and 8:00 PM) to cats experimentally inoculated with FHV-1. Cats in that study[12] that received famciclovir had significantly better systemic, ophthalmic, clinicopathologic, virologic, and histologic outcomes than did placebo-treated cats. A case series report[16] described improvement of clinical signs following administration of famciclovir (62.5 mg [8 to 21 mg/kg {3.6 to 9.5 mg/lb}], PO, q 12 to 24 h) to client-owned cats with spontaneously occurring conjunctivitis, keratitis, or rhinosinusitis attributed to FHV-1. In the same report,[16] administration of famciclovir (125 mg [30 mg/kg {13.6 mg/lb}], PO, q 8 h) improved clinical signs in cats with spontaneously occurring dermatitis attributed to FHV-1.

The purpose of the study reported here was to retrospectively assess the outcomes of cats that received orally administered famciclovir 3 times/d for treatment of spontaneously occurring disease (ocular, respiratory, or dermatologic conditions, alone or in combination) attributable to naturally acquired FHV-1 infection, to compare results between cats that received low (approx 40 mg/kg, 3 times/d) versus high (approx 90 mg/kg, 3 times/d) dosages of famciclovir, and to evaluate owner perceptions regarding treatment and outcome in famciclovir-treated cats by means of a written survey. On the basis of available data, we hypothesized that famciclovir treatment would result in resolution of clinical signs with minimal or no adverse effects in cats with spontaneously occurring herpetic disease, that results would be comparable when famciclovir was administered at 40 or 90 mg/kg 3 times/d, and that owners would be satisfied with the outcome of famciclovir treatment.

Materials and Methods

Case selection

Electronic medical records of the University of California-Davis Veterinary Medical Teaching Hospital from June 1, 2006, through May 30, 2013, were searched to identify cats treated with famciclovir. The search terms included famciclovir, Famvir, and famcyclovir. Following electronic retrieval, each record was individually reviewed to ensure that it described a cat with spontaneously occurring ocular, respiratory, or dermatologic disease, alone or in combination, attributed to suspected FHV-1 infection that was treated with famciclovir PO 3 times/d, and that results of ≥ 1 follow-up examination after initiation of treatment were available for review.

Medical records review

Information retrieved from the electronic medical record included patient sex, breed, age, and body weight; history of ophthalmic or other disease; treatment immediately prior to evaluation at the study hospital; physical examination (including ophthalmic) findings; and types and results of diagnostic tests performed. Clinical diagnosis, medical treatments provided, source of the famciclovir administered, surgical procedures performed, clinical outcomes, and follow-up time were also recorded.

Famciclovir administration

Dosages of famciclovir administered to cats were determined on the basis of data available at the time the patient was seen. Therefore, from June 2006 through May 2009, cats were prescribed famciclovir at a targeted dosage of 90 mg/kg 3 times/d[12] (no cats met inclusion criteria between May and September 2009). In September 2009, data from 2 studies[13,16] involving cats led to a reduction of the targeted dosage to 40 mg/kg 3 times/d; results of 1 study[13] revealed equivalent penciclovir pharmacokinetics for a single dose of famciclovir at 40 or 90 mg/kg, and findings in the other, a case series investigation,[16] suggested that famciclovir was efficacious at dosages < 90 mg/kg 3 times/d.

For all cats, famciclovir treatment was started and discontinued at the discretion of the attending clinician in consultation with the client. Cessation of treatment typically occurred following complete resolution of clinical signs or if no improvement in clinical signs was observed after a course of treatment was believed to be sufficient on the basis of experience with similar cases. Reinstitution of treatment occurred if patients had a recurrence of clinical signs or new signs attributable to FHV-1 infection; the number of treatments that each cat required during the follow-up period was recorded.

Data handling

Because cats were administered commercially available tablets, there was some body weight–dependent variation from the targeted dosages. Therefore, for data analysis, cats were assigned to 1 of 2 treatment groups: a low-dose group that received approximately 40 mg of famciclovir/kg 3 times/d and a high-dose group that received approximately 90 mg of famciclovir/kg 3 times/d. Additionally, for data analysis, patients were considered juvenile if they were < 7 months of age, adult if they were ≥ 7 months and < 10 years of age, and geriatric if they were ≥ 10 years of age.

An overall disease severity score (1 = mild, 2 = moderate, and 3 = severe) was subjectively assigned on the basis of the attending clinician's description in the medical record of the most severely affected tissue at the time of the initial physical examination and at recheck examinations. The score was retrospectively assigned to each patient by 1 veterinary ophthalmologist (SMT) who reviewed all records but was not masked to treatment group. Clinical improvement was defined as mild or marked if, at the first recheck examination, disease severity scores had decreased by 1 or ≥ 2 grades, respectively. Clinical im-

provement was graded as nonapparent if no change was noted or disease severity worsened between the initial and final visit during the famciclovir administration period.

The duration of clinical signs was calculated from the patient's medical record. The time to clinical improvement was defined as the interval from initiation of famciclovir treatment to the first recheck examination when improvement was recorded; cats without apparent improvement were excluded from this analysis. Time to onset of adverse effects was the interval from initiation of famciclovir treatment to the first date that the adverse effect was observed by the owner or clinician. Follow-up time was the interval from initiation of famciclovir treatment to the last follow-up visit; the last date that medical records were searched for follow-up was July 1, 2014.

Owner survey

A survey designed to assess owner perceptions of convenience and cost of treatment, as well their pet's response to treatment and subsequent outcome, was mailed via US Postal Service to owners of all cats identified during the medical record review. The University of California-Davis Internal Review Board deems surveys of this nature as exempt from approval. Prior to mailing, the survey was assessed by a veterinary ophthalmologist and an ophthalmology resident in training at the study facility and by 1 owner of a cat receiving famciclovir. Because cats were continually added to this study, owners were surveyed in 3 separate cohorts (June 1 through 30, 2009; April 1 through 30, 2011; and October 1 through 31, 2013). The survey wording and format were identical in all cases, except that the survey was personalized for each client (the medication list was individualized for the patient that was the subject of the survey questions); a generic copy of the survey is provided (**Supplemental Appendix S1**, available at avmajournals.avma.org/doi/suppl/10.2460/javma/249.5.526). On each occasion, a cover letter explaining the purpose of the study and requesting owner participation, the survey, and a stamped, addressed return envelope were mailed to owners of all cats identified as meeting study inclusion criteria (with each cat included only once in the study). The cover letter indicated that owner responses, although not confidential, would not be included in the medical records of any of their pets and would not affect further treatment that their cat received, but would be used in an anonymous manner. The cover letter also stated that the survey regarded treatment of FHV-1 and client satisfaction; however, famciclovir was not specifically mentioned. Owners of cats from all 3 cohorts who did not respond to the survey received a second mailing containing the same cover letter and survey, plus a second stamped, addressed return envelope. Owners who failed to respond to either mailed solicitation were contacted via telephone and asked to return the completed survey by mail or offered the opportunity to complete the survey via telephone. If owners preferred to complete the survey by telephone, all questions were read verbatim from the survey without any attempt to elicit or bias the respondent's answers.

The survey comprised 10 questions (multiple choice, open-ended, or both) specific to the patient's treatment at the study hospital. Respondents were asked to recall the clinical signs that prompted them to bring their cat to our facility and to use semiquantitative scales (1 [mild] through 10 [severe]) to rate severity of their cat's illness prior to treatment and after treatment was completed. Respondents were asked to provide an opinion regarding the permanency of improvement (permanent, temporary, or no improvement; if temporary, a space was provided for the respondent to indicate the duration of improvement after treatment was stopped), to rank (from 1 [most effective] to 3 [least effective]) all medications prescribed at the initial visit, and to note (yes or no) whether any adverse effects (described for the clients as side effects) had been noticed that could be attributable to any of the listed medications. If adverse effects were noted, respondents were asked to indicate the drug they thought caused the effect, to describe their observation, to indicate the time of onset relative to the start of drug administration and the duration of the signs, and to grade the severity of the adverse effect on a semiquantitative scale (1 [mild] through 10 [severe]). They then were asked whether, considering all visits to the study hospital and all drugs prescribed, they thought the treatments were cost-effective (yes or no, with an open field to allow comments on excessive costs) and whether, if the same circumstances arose again, they would be willing to have their cat undergo similar or identical treatments (yes, no, or unsure, with an open field to allow explanation for the response). The answer to this question was used to define the overall outcome of treatment as successful or unsuccessful for a given patient. A semiquantitative scale (1 [not important] through 10 [very important]) was provided for respondents to indicate the importance of each of the following factors in their willingness to have the cat treated in the same manner again: cost, degree of improvement in the cat's illness, ease of giving eye medications, ease of giving oral medications, and number of recheck appointments (followed by an open field for comments on other factors). A final question asked for any further comments or suggestions that the respondent felt would be useful to owners of cats being treated for feline herpesvirus infections.

Statistical analysis

Categorical variables (sex and breed of cats, concurrent surgical interventions performed, adverse effects observed, whether the owner responded to the survey [yes or no], clinical signs that prompted the patient evaluation, and whether treatment outcome was successful or unsuccessful according to owner survey responses) were compared between cats in the low-

dose and high-dose famciclovir groups by means of a Fisher exact test.[a] Body weight data were normally distributed (Shapiro-Wilk test) and were compared between dose groups with a Student *t* test.[b] Nonnormally distributed continuous variables (age, duration of clinical signs, follow-up time, famciclovir treatment duration, number of courses of famciclovir, disease severity score at study inclusion, and owner-reported importance of factors that would influence their willingness to have the cat undergo the same treatment again) were compared between cats that received low versus high doses of famciclovir by use of a Mann-Whitney rank sum test.[b] A Mann-Whitney rank sum test was also used to compare responses from owners who completed the survey after 1 request versus those respondents who required > 1 request. Clinical improvement (mild, marked, or none; transformed for analysis as 1, 2, or 0) was assessed by a nonparametric trend test and a Kruskal-Wallis test.[c] A Wilcoxon signed rank test was used to test the difference in the number of medications prior to and immediately following inclusion into the study (ie, the time of initiation of famciclovir treatment, 3 times/day at the study institution). Cox regression[c] and linear regression[b] were used to assess the relationship between famciclovir dose (high vs low) and time to improvement. Ordered logistic regression[c] was performed to determine any independent effects for age, breed, sex, disease severity at study inclusion, duration of clinical signs, follow-up time, famciclovir treatment duration, number of courses of famciclovir treatment, or concurrent surgical intervention on clinical improvement in addition to the primary effect of dose. Time to clinical improvement was also compared between low- and high-dose treatment groups with Kaplan-Meier survival analysis and the log-rank test.[c] For all analyses, values of $P < 0.05$ were considered significant.

Results

Cats and treatment history

The automated search of electronic medical records for the keywords famciclovir, Famvir, or famcyclovir yielded the records of 80 cats; 59 met the study inclusion criteria. The study population included 27 (46%) castrated males, 9 (15%) sexually intact males, 19 (32%) spayed females, and 4 (7%) sexually intact females. The most commonly represented breeds were domestic shorthair (39/59 [66%]), Persian (5 [8%]), Himalayan (4 [7%]), and Burmese (3 [5%]). Other breeds included Abyssinian, American Shorthair, Devon Rex, Main Coon Cat, Ragdoll, Siamese, Scottish Fold, and Sphinx (1 [2%] each). The low-dose group comprised 33 cats, and the high-dose group comprised 26 cats. The median duration of clinical signs prior to inclusion in the study (ie, first administration of famciclovir, 3 times/day at the study institution) was 40 days (range, 0 to 2,154 days); 15 cats had had clinical signs for ≥ 180 days. There was no significant difference between the low-dose and high-dose famciclovir treatment groups with respect to sex distribution ($P = 0.409$), distribution of domestic versus purebred cats ($P = 0.409$), median age ($P = 0.384$), body weight, ($P = 0.080$) or duration of clinical signs ($P = 0.152$) at the time of study inclusion **(Table 1)**.

Prior to inclusion in the study, 9 cats were receiving no medications, and 50 cats were receiving ≥ 1 topical ophthalmic or systemically administered

Table 1—Summary (No. [%] or median [range]) data for variables of interest in a retrospective study of 59 cats that were treated with famciclovir at approximately 40 mg/kg (18 mg/lb; low dose) or 90 mg/kg (41 mg/lb; high dose), PO, 3 times/d for presumed FHV-1 infection between June 1, 2006, and May 30, 2013.

		Famciclovir dose			
Variable	**All cats (n = 59)**	**Low (n = 33)**	**High (n = 26)**	**Juvenile (n = 22)**	**Geriatric (n = 14)**
Sex					
Male	36 (61)	21	15	6	8
Female	23 (39)	12	11	6	6
Breed					
Domestic shorthair	39 (66)	20	19	12	8
Purebred	20 (34)	13	7	0	6
Age (y)	6.0 (0.03–16)	7.0 (0.1–15)	4.5 (0.03–16)	0.12 (0.03–0.54)	13.4 (10.0–16.0)
Body weight (kg)	4.2 (0.2–10)	4.2 (0.4–10)	4.2 (0.2–7.1)	0.4 (0.2–3.8)	4.4 (2.7–10)
Duration of clinical signs prior to initial examination (d)	40 (0–2154)	75 (0–2154)	22 (2–548)	5 (2–30)	43 (7–189)
Famciclovir dose (mg/kg)	60 (30–140)	44 (30–63)	91 (70–140)	99 (40–140)	69 (33–96)
Treatment duration (d)	24 (4–882)	36 (4–464)	14 (7–882)*	8 (7–189)	41 (4–232)
Time to clinical improvement (d)	13 (3–183)	14 (7–183)	7 (3–28)*	7 (3–14)	13 (4–40)

Cats < 7 months of age and ≥ 10 years of age were considered juvenile and geriatric, respectively. Treatment duration and time to improvement were measured from initiation to termination of the described famciclovir treatment and from initiation of treatment to the first visit where clinical improvement was documented, respectively. Results for the low- and high-dose famciclovir treatment groups were compared with a Fisher exact test (sex and breed), Student *t* test (body weight), or Mann-Whitney rank sum test (all other variables).

*Value differs significantly ($P < 0.05$) from that for cats in the low-dose group.

To convert mg/kg to mg/lb, divide by 2.2.

drug (median, 2; range, 1 to 6). Twenty-nine of 50 cats were receiving 1 systemic antiviral drug (L-lysine [n = 28] or famciclovir [5], PO, or feline Ω-interferon [1], SC); 4 cats were receiving both lysine and famciclovir and 1 cat was receiving both lysine and feline Ω-interferon. Eighteen cats were receiving a topical antiviral ophthalmic medication (cidofovir [n = 10], idoxuridine [7], or vidarabine [1]); 1 cat received a topical dermal antiviral medication (human α-interferon). Sixteen cats were receiving antiviral drugs via both systemic and topical routes.

Each of the 5 cats receiving famciclovir prior to study inclusion was administered a different dosage (5 mg/kg [2.3 mg/lb], 16 mg/kg [7.3 mg/lb], or 39 mg/kg [17.7 mg/lb], PO, once daily; or 10 mg/kg [4.5 mg/lb] or 75 mg/kg [34.1 mg/lb], PO, 2 times/d). Four additional cats had received famciclovir at some point prior to referral but had treatment discontinued; dosages for these cats were 93 mg/kg (42.3 mg/lb), PO, 2 times/d (this treatment was a compounded suspension and was discontinued because of drooling and vomiting); 19 mg/kg (8.6 mg/lb), PO, 2 times/d; 25 mg/kg (11.4 mg/lb), PO, 3 times/d; or 107 mg/kg (48.6 mg/lb), PO, 2 times/d.

Prior to study inclusion, 15 cats were receiving systemic (orally administered) antimicrobials, including doxycycline (n = 7), amoxicillin-clavulanate (7), and metronidazole (1). Thirty-four cats were receiving 1 topical ophthalmic antimicrobial treatment (most commonly oxytetracycline-polymyxin B [n = 10], erythromycin [7], or ofloxacin [6]), and 1 cat was receiving 2 topical ophthalmic antimicrobial treatments. Five cats were receiving orally administered anti-inflammatory and immunosuppressive medications (including prednisolone [n = 3] and megestrol acetate [2]); 1 cat was receiving tacrolimus topically, and 1 of the 3 receiving oral prednisolone treatment also had prednisolone administered topically. Medications of other classes were being administered orally to 4 cats, and 12 cats were receiving other topical medications, serum, or sodium chloride ointment.

Examination findings and diagnostic tests

Ophthalmic signs were observed in both eyes of 31 of 59 (53%) cats, in the left eye only of 13 (22%), and in the right eye only of 11 (19%). The remaining 4 cats had rhinitis (2/59 [3%]) or dermatitis (2 [3%]) only. Most cats had > 1 clinical sign. The most common abnormalities noted on clinical examination were conjunctivitis (51/59 [86%]); keratitis (51 [86%]); blepharitis (19 [32%]); nasal discharge, sneezing, or both (10 [17%]); and dermatitis (4 [7%]). Specific corneal abnormalities found in ≥ 1 eye were ulcerative keratitis (42/59 [71%]), corneal sequestration (12 [20%]), dendritic corneal ulcers (9 [15%]), eosinophilic keratitis (4 [7%]), or symblepharon (4 [7%]). Schirmer tear test-1 was performed in 9 cats (4 cats in the low-dose group and 5 in the high-dose group for famciclovir treatment); results were within the reference range (11 to 23 mm/min)[17] for 4 of these and less than the lower reference limit in ≥ 1 eye for the remaining 5. Median Schirmer tear test-1 values for cats with results within and below the reference range were 15 mm/min (range, 11 to 18 mm/min) and 8 mm/min (range, 2.5 to 9 mm/min), respectively. Intraocular pressure was measured in 16 cats; the median value was 16 mm Hg (range, 11.5 to 25 mm Hg). Intraocular pressure was within the reference range (15 to 25 mm Hg)[18] in 7 patients, low in ≥ 1 eye of 8 patients, and high in 1 eye of 1 patient. Fluorescein stain was applied to both eyes of 55 of 59 (93%) cats and was retained by the cornea of ≥ 1 eye in 39 of 55 (71%).

Additional tests, including a PCR assay targeting FHV-1 DNA, cytologic or histologic examination of samples from the cornea, conjunctiva, or haired skin (or some combination of these), and aerobic microbial culture to assess for an etiologic diagnosis were performed for 26 of 59 (44%) cats. A PCR assay targeting FHV-1 DNA was performed for 10 of 59 (17%) cats, with positive results for 6 of 10.

Cytologic examinations were performed on slides of conjunctival (n = 2) or corneal (8) swab samples from 10 cats. Nine of 10 had hyperplastic epithelium of varying severity, with occasional melanin granules identified in 1. Degenerate neutrophils and bacteria were evident in both conjunctival samples (extracellular in one cat and location not recorded in the other); one cat also had eosinophils, mast cells, and erythrocytes present, whereas the other had reactive lymphocytes detected. Three of 8 corneal samples included degenerate neutrophils, with extracellular bacteria identified in 1. One of 8 corneal samples had neutrophils, eosinophils, mast cells, and melanocytes present, and 1 had neutrophils and erythrocytes identified.

Histologic examinations were performed on biopsy samples from the conjunctiva (n = 4) or haired skin (2) of 6 cats. Hyperplastic epithelium was present in one conjunctival sample, and intranuclear epithelial cell inclusion bodies and epithelial erosion was identified in another. Neutrophils, lymphocytes, and plasma cells were present in 3 of 4 conjunctival samples; 1 of these 3 cats also had macrophages present, 1 had mast cells present, and another had eosinophils, mast cells, and Mott cells identified. Both biopsy examinations of haired skin revealed ulceration and intracellular bacteria; 1 cat had macrophages, plasma cells, eosinophils, and mast cells observed, and 1 had degenerate neutrophils, degenerate eosinophils, and intranuclear epithelial cell inclusion bodies present.

Aerobic bacterial culture of a corneal sample was performed for 10 of 59 (17%) cats, and organisms were identified as *Mycoplasma* spp (n = 2) or coagulase-positive *Staphylococcus* sp (1) in 3 of 10 cats. Aerobic bacterial culture of dermal tissue was performed for 1 cat, with *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus pseudintermedius* isolated. Six cats had fungal cultures of corneal (n = 5) or dermal (1) samples performed with no growth identified.

Treatment and follow-up

The manufacturer of famciclovir administered to cats was identified in 59% of cases (with 17/59 [29%] receiving a drug manufactured by one source [source A][d] and 17 [29%] receiving a drug manufactured by another source [source B][e]); manufacturer information was not available for 24 (41%) patients, and 1 received formulations from 2 different sources during the treatment. Cats in the low-dose group (n = 33) received a median famciclovir dosage of 44 mg/kg (20 mg/lb; range, 30 to 63 mg/kg [13.6 to 28.6 mg/lb]), PO, 3 times/d, whereas those in the high-dose group (n = 26) received a median dosage of 91 mg/kg (41.4 mg/lb; range, 70 to 140 mg/kg [31.8 to 63.6 mg/lb]), PO, 3 times/d (Table 1). One cat was initially administered famciclovir at 45 mg/kg (duration, 27 days) and was subsequently given an 89 mg/kg dose (duration, 48 days) because of perceived lack of efficacy of the drug at the lower dose. For data analysis, this cat was included in the 90 mg/kg dose group. The median duration of treatment was significantly ($P < 0.001$) longer for cats in the low-dose group than for those in the high-dose group. There was a significant ($P < 0.001$) association between dose group and the source of famciclovir, with a greater proportion of cats in the high-dose group (15/18) receiving famciclovir from source A[d] than cats in the low-dose group (2/16). Cats were prescribed a median of 3 additional medications (range, 0 to 6) at the time famciclovir treatment (3 times/d) was initiated at the study facility; in some cats, this was a continuation of treatment prescribed by the referring veterinarian. Twenty-nine cats received L-lysine PO, 14 cats received a topical antiviral medication (idoxuridine [n = 10] or cidofovir [4]), and 17 cats were given antimicrobials PO (amoxicillin-clavulanate [7], doxycycline [6], or metronidazole, azithromycin, cefpodoxime, or pradofloxacin [1 each]). Topically administered antimicrobials included ciprofloxacin, ofloxacin, erythromycin, oxytetracycline-polymyxin B, tobramycin, cefazolin, neomycin-polymyxin B with bacitracin or gramicidin, and gentamicin; 43 cats received one of these agents, and 4 cats each received 2. Six cats received prednisolone PO (n = 5) or topically (1), and 1 cat was treated with cyclosporine topically. Thirty-two cats received additional medications PO, topically, or by both routes. Oral medications included buprenorphine (n = 6), tramadol (3), chlorpheniramine (1), and acepromazine (1); topical treatments included sodium hyaluronate (n = 14), atropine (13), and serum (6). For the 50 cats receiving medications prior to inclusion in the study, the median change in number of medications was 0 (range, −3 to 5) at the time of study inclusion. Furthermore, 32 of the 50 (64%) cats were prescribed fewer (n = 17) or the same number of (15) medications at study inclusion versus prior to initiation of the study.

Concurrent with famciclovir administration, 14 of 59 (24%) cats underwent a surgical intervention. These included conjunctival island graft (n = 3), conjunctival pedicle flap (2), superficial keratectomy with a bioscaffold graft of decellularized porcine bladder[f] (2), symblepharon repair (2), or superficial keratectomy with corneoconjunctival transposition, superficial keratectomy with partial lateral temporary tarsorrhaphy, Hotz-Celsus procedure, superficial keratectomy alone, or enucleation (1 each). The proportion of cats that underwent surgical intervention did not differ significantly ($P = 0.227$) between the high-dose and low-dose famciclovir treatment groups (4/26 and 10/33, respectively).

The median duration of follow-up for all cats was 22 weeks (range, 1 to 304 weeks). There was no significant ($P = 0.697$) difference in follow-up time between cats in the high-dose (median, 22 weeks; range, 1.0 to 304 weeks) and low-dose (median 22 weeks; range, 1.9 to 188 weeks) famciclovir treatment groups. Following oral administration of famciclovir at any dose tested, improvement in clinical signs was retrospectively rated as marked in 30 of 59 (51%) cats and mild in 20 (34%) cats at the first visit that improvement was documented and nonapparent in 9 (15%) cats at the final visit prior to discontinuation of famciclovir **(Figure 1)**. Cats in the high-dose group had significantly ($P = 0.025$) greater improvement in clinical signs than did cats in the low-dose group **(Figure 2)**. Of 14 geriatric cats, clinical improvement following famciclovir administration was judged as marked in 7, mild in 4, and nonapparent in 3. Among 12 juvenile cats, clinical improvement was marked in 10 and mild in 2.

Of the 50 cats with improvement in clinical signs, the median time from initiation of famciclovir 3 times/d to improvement was significantly ($P < 0.001$) shorter for those in the high-dose versus low-dose famciclovir treatment groups (Table 1; **Figure 3**). There was also a positive correlation between dose and time to improvement when dose was assessed as a continuous variable ($R^2 = 0.119$; $P = 0.014$) by linear regression. Of the 9 cats with no apparent improvement, subsequent diagnoses included periocular *Malassezia* dermatitis with mucocutaneous pyoderma (n = 1), restrictive orbital myofibroblastic sarcoma (1), ulcerative bacterial keratitis (2), presumptive chlamydial conjunctivitis (1), corneal sequestra (2), eosinophilic keratoconjunctivitis (1), or ulcerative herpetic dermatitis (1). The cat with restrictive orbital myofibroblastic sarcoma was described in a separate publication.[19]

Of the 59 study cats, 44 (75%), 13 (22%), or 2 (3%) received 1, 2, or 3 courses of famciclovir treatment, respectively; the number of treatment courses did not differ significantly ($P = 0.636$) between the low-dose (median, 1; range, 1 to 3) and high-dose (median, 1; range, 1 to 2) famciclovir treatment groups. The number of recheck appointments in the follow-up period also did not differ between the low-dose (median, 4; range, 1 to 28) and high-dose (median, 4; range, 1 to 23) groups ($P = 0.689$).

Age ($P = 0.360$), breed ($P = 0.203$), sex ($P = 0.627$), disease severity ($P = 0.436$), duration of her-

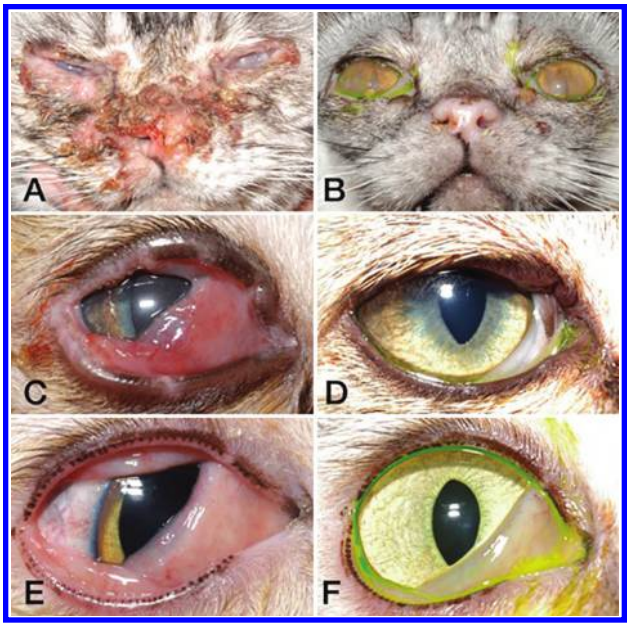

Figure 1—Photographs of 3 domestic shorthair cats before and after treatment with famciclovir for presumed FHV-1 infection. An overall disease severity score (1 = mild, 2 = moderate, and 3 = severe) was retrospectively assigned on the basis of the attending clinician's description of the most severely affected tissue at the time of famciclovir treatment initiation and again at the first visit where improvement was noted; clinical improvement, when present, was defined as mild or marked if scores on the recheck examination were improved by 1 or ≥ 2 grades, respectively. A and B—A 15-year-old spayed female cat that was evaluated because of severe blepharitis, conjunctivitis, and eosinophilic keratitis in both eyes as well as ulcerative herpetic facial dermatitis. Images were obtained before (A) and after (B) 30 days of treatment with famciclovir at 93 mg/kg (42.3 mg/lb), PO, 3 times/d. The cat was categorized as having marked clinical improvement. C and D—A 2-month-old sexually intact male cat that had marked conjunctival hyperemia, chemosis, and symblepharon formation in the right eye prior to treatment (C) and had complete resolution of all 3 conditions without surgical intervention after 17 days of treatment with famciclovir at 62.5 mg/kg (28.4 mg/lb), PO, 3 times/d (D). This cat was also classified as having marked clinical improvement. E and F—A 1.5-year-old spayed female cat with moderate conjunctival hyperemia and chemosis in the right eye before treatment (E) and mild conjunctival hyperemia and chemosis with focal, superficial ulcerative keratitis after treatment (F) for 11 days with famciclovir at 47 mg/kg (21.4 mg/lb), PO, 3 times/d. This cat was classified as having mild clinical improvement.

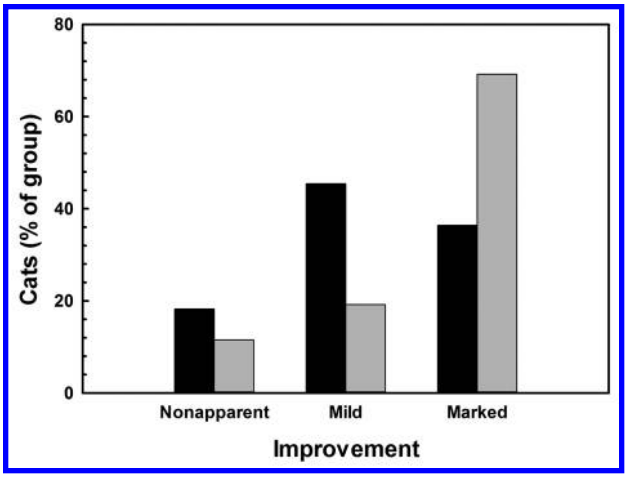

Figure 2—Percentages of cats in each clinical improvement category after treatment with famciclovir for presumed FHV-1 infection. Cats in the low-dose group (black bars; n = 33) received approximately 40 mg of famciclovir/kg, PO, 3 times/d (18 mg/lb), and cats in the high-dose group (gray bars; 26) received approximately 90 mg of famciclovir/kg (41 mg/lb), PO, 3 times/d. Cats treated in the high-dose group had significantly (P = 0.041 or P = 0.025) greater improvement than did cats in the low-dose group (nonparametric trend test and Kruskal-Wallis test, respectively). ***See*** Figure 1 for remainder of key.

petic signs (P = 0.410), follow-up time (P = 0.746), famciclovir treatment duration (P = 0.116), number of courses of famciclovir treatment (P = 0.918), or concurrent surgical interventions (P = 0.370) had no independent effects on improvement in logistic regression analysis when the primary effect of dose was controlled for in the model.

Adverse effects

Forty-nine of 59 (83%) study cats had no adverse effects observed, including 8 patients that received famciclovir for > 3 months and 1 cat that received 100 mg/kg (45.5 mg/lb), PO, 3 times/d for 2.4 years. Adverse effects potentially associated with the drug were reported for 10 (17%) cats during famciclovir treatment; these included diarrhea (n = 4), anorexia (2), polydipsia with a decreased USG (compared with a pretreatment value; 1), polydipsia with a USG considered normal (1), vomiting (1), a 6% decrease in body weight (from 3.5 to 3.3 kg [7.7 to 7.3 lb]; 1), and increased frequency of hiding behavior that the owner attributed to pill administration (1). At the onset of adverse effects, famciclovir administration was immediately discontinued for 7 of 10 cats, including 5 with gastrointestinal signs, 1 cat with polydipsia and decreased USG, and 1 with increased hiding behavior. The treatment was continued in cats with transient diarrhea (n = 2) and polydipsia with no change in USG (1). Gastrointestinal signs resolved in 4 patients that had famciclovir treatment discontinued and had a follow-up visit at the study hospital. Polydipsia resolved following drug discontinuation in 1 cat that was receiving 85 mg of famciclovir/kg (38.6 mg/lb); however, the USG remained low in subsequent urinalyses performed 9, 17, 26, and 37 months after the famciclovir treatment ended. At the 37-month follow-up visit, this cat was diagnosed as having stage II chronic kidney disease as defined by the International Renal Interest Society system. Following initiation of famciclovir treatment at the study hospital, 9 cats had a CBC performed, 9 had a serum biochemical analysis, and 7 had a urinalysis; results of the same test performed prior to initiation of famciclovir were available for comparison in 4, 4, and 1 of these cats,

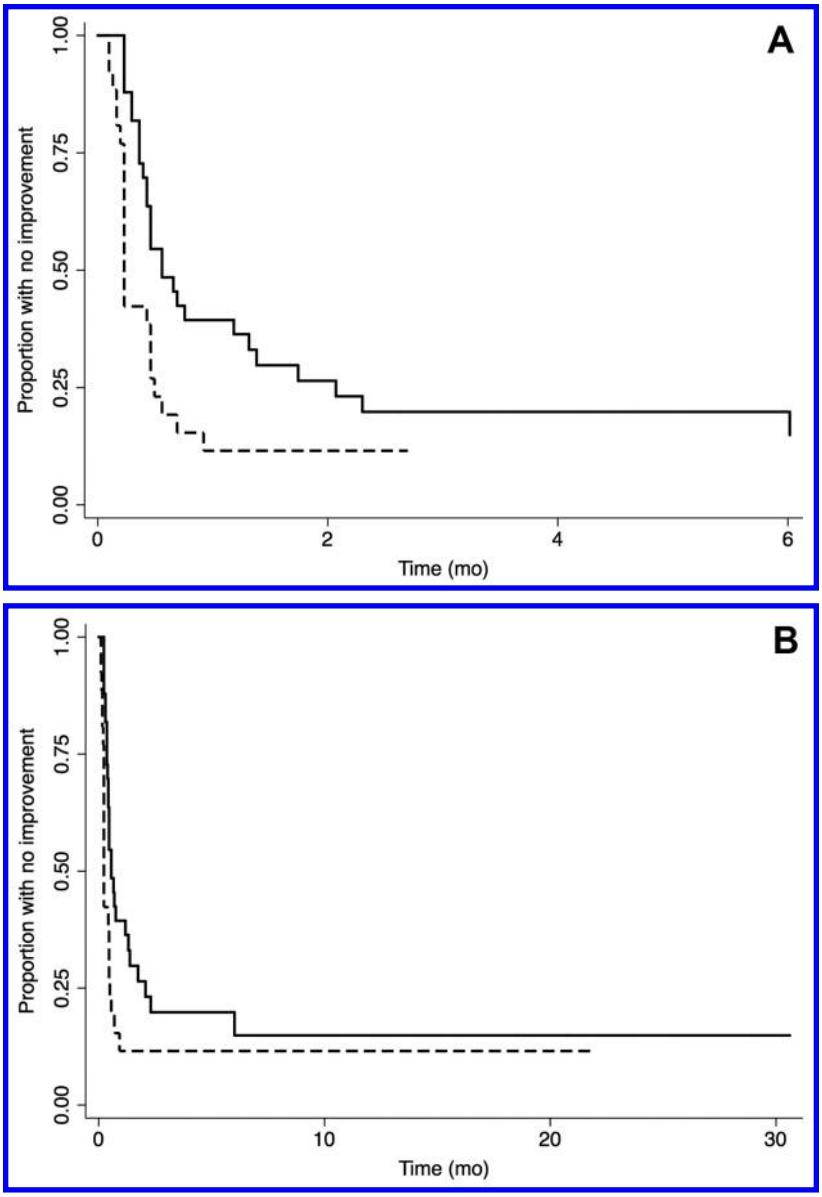

Figure 3—Kaplan-Meier plots comparing the time to improvement of clinical signs after initiation of famciclovir treatment (3 times/d) in cats of the low-dose (solid line; n = 33) and high-dose (dashed line; 26) famciclovir treatment groups during the first 6 study months (A) or throughout the entire follow-up period (B). Cats in the high-dose group had a significantly (P = 0.003) shorter time to improvement than did cats in the low-dose group (Cox regression).

respectively. The cat that developed polydipsia and decreased USG during famciclovir treatment had mild azotemia (BUN concentration, 50 mg/dL; reference range, 18 to 33 mg/dL) with a USG considered normal (1.036) 1 month prior to initiation of famciclovir. After 35 days of treatment with famciclovir, the patient's BUN concentration and USG decreased to 36 mg/dL and 1.026, respectively. Mild azotemia (BUN concentration, 40 mg/dL) was detected in 1 other cat prior to initiation of famciclovir treatment at 44 mg/kg, PO, 3 times/d and again after 8 days of the treatment (BUN concentration, 42 mg/dL); famciclovir was continued for 16 additional days, and no azotemia was identified 57 days after discontinuing famciclovir (BUN concentration, 30 mg/dL). One cat with a BUN concentration within the reference range (30 mg/dL) prior to initiation of famciclovir treatment at 49 mg/kg (22.3 mg/lb), PO, 3 times/d developed polydipsia and mild azotemia (BUN concentration, 40 mg/dL) with an appropriate USG (1.042) after 13 days of treatment; famciclovir administration was continued in this patient, but no further clinical chemistry values were available. Serum creatinine concentration remained within the reference range for all 4 patients that had data available for review from before and after initiation of famciclovir treatment. Sporadic values outside of the reference ranges were noted for some variables assessed with the CBC, serum biochemical analysis, and urinalysis for these patients, but clinically important differences were not detected between time points before and after initiation of famciclovir treatment.

Median time to adverse effects in cats receiving famciclovir was 18 days (range, 3 to 36 days) from the time that the 3 times/d treatment was initiated. No significant (P = 1.0) difference in the occurrence rate of observed adverse effects was detected between cats in the low-dose (6/33 [18%]) and high-dose (4/26 [15%]) treatment groups. Five of the 10 cats that had adverse effects reported were geriatric; none was juvenile.

Surveys

Thirty-two of 59 (54%) owners of cats in the study completed the survey. Of 23 surveys mailed in June 2009, 5 (22%) were returned after the first mailing and 1 (4%) was returned after the second mailing; 3 (15%) were completed by telephone. For the April 2011 survey, 17 surveys were mailed, with 8 (47%) returned after the first mailing, 1 (6%) returned after the second mailing, and 5 (29%) completed by telephone. Nineteen surveys were sent to the final cohort in October 2013, with 5 (26%) returned after the first mailing, 1 (5%) returned after the second mailing, and 3 (16%) returned after a follow-up telephone call; none of these was completed by telephone. Not all respondents answered every question.

Differences in major outcome variables such as owner assessment of the importance of cost (P = 0.414), degree of illness improvement (P = 0.154),

ease of giving eye medications (P = 0.068), ease of giving oral medications (P = 0.149), and number of recheck examinations (P = 0.284) were not detected between those owners who completed the survey after 1 versus multiple requests. Accordingly, data provided by respondents after 1 or multiple requests were combined for all analyses. Response rates did not differ significantly (P = 0.122) between owners of cats in the low-dose (21/33 [64%]) and high-dose (11/26 [42%]) famciclovir treatment groups. The reasons for which cats were brought to the study hospital were not significantly ($P \geq 0.197$ for all comparisons) different between owners of cats in the low-dose or high-dose treatment groups **(Table 2)**.

The owner-assessed disease severity score for all cats at completion of famciclovir treatment (median, 2; range, 1 to 8) was significantly ($P < 0.001$) lower than at initiation of treatment (median, 8; range, 3 to 10). Owners characterized their cats' clinical signs as permanently improved (17/32 [53%]), temporarily improved (8 [25%]), stable (1 [3%]), or not improved (1 [3%]); some wrote in answers rather than selecting from the options provided. Five (16%) owners did not answer the question. Of the 8 owners who characterized the improvement as temporary, 6 reported a duration of improvement (median, 12 months; range, 0.5 to 12 months) and 2 did not answer the question. By use of each owner's response to the survey question in which they were asked whether, given their experience and current knowledge and if the same circumstances arose again, they would be willing to have the cat undergo similar or identical treatment, 29 of 32 (91%) owners were classified as satisfied, 2 (6%) as unsure, and 1 (3%) as dissatisfied. Of the 3 owners who were not classified as satisfied, the reasons provided included cost (n = 1) or inability to cure the condition (1); 1 owner (who reported being unsure) did not indicate a reason. Eleven of 11 owners of cats in the high-dose treatment group and 18 of 21 (86%) owners of cats in the low-dose treatment group were classified as satisfied, with no significant (P = 0.534) difference between the 2 groups. There was also no significant difference between owners of cats in the low-dose and high-dose treatment groups for rankings of the importance of cost, degree of improvement in the cat's illness, ease of giving eye medications, ease of giving oral medications, and number of recheck examinations in regard to their willingness to have the cat treated the same way again **(Table 3)**.

Table 2—Owner-reported factors that prompted evaluation at the study facility for 32 of the 59 cats in Table 1 for which surveys were completed.

Factor	All respondents (n = 32)	Patient's famciclovir dose		*P* value
		Low (n = 21)	High (n = 11)	
Painful (squinting) eye or eyes	21 (66)	14 (67)	7 (64)	1.000
Discharge or drainage from eye or eyes	24 (75)	14 (67)	10 (91)	0.209
Poor response to previous treatments	19 (59)	12 (57)	7 (64)	1.000
Sneezing or nasal discharge	7 (22)	3 (14)	4 (36)	0.197
Cat was less active	5 (16)	2 (10)	3 (27)	0.310
Eye or eyes appeared cloudy or opaque	17 (53)	13 (62)	4 (36)	0.266
Eye or eyes appeared red	13 (41)	8 (38)	5 (45)	0.721

Owners of all study cats were sent a 10-question survey by US postal mail with a cover letter asking that they complete the questionnaire to provide their views on the efficacy, convenience, cost, and outcome of their cat's treatment. Most (24/32) respondents completed the written survey; 8 completed the survey by telephone with the questions read and answers recorded by an investigator. In this section of the survey, owners were asked to select (from a list) all factors that prompted them to have their cat seen at the study hospital. Results are reported as number (%) of responses for the group; *P* values reflect results of comparison between responses selected by owners of cats in the high-dose and low-dose treatment groups (Fisher exact test).

See Table 1 for remainder of key.

Table 3—Median (range) of importance rankings for various factors provided by the same 32 cat owners as in Table 2 in regard to their willingness to have the cat treated in the same manner again.

Factor	All respondents (n = 32)	Patient's famciclovir dose		*P* value
		Low (n = 21)	High (n = 11)	
Cost	8 (1–10)	8 (1–10)	6 (1–10)	0.173
Degree of improvement in the cat's illness	10 (9–10)	10 (9–10)	10 (9–10)	1.000
Ease of giving eye medications	6 (1–10)	6 (1–10)	6 (1–10)	0.625
Ease of giving oral medications	6 (1–10)	6 (1–10)	6 (1–10)	0.285
No. of recheck appointments	5 (1–10)	5 (1–10)	3 (1–9)	0.707

The described factors were ranked by owners on a semiquantitative scale from 1 (not important) to 10 (very important); *P* values reflect results of comparison between rankings by owners of cats in the high-dose and low-dose treatment groups (Mann-Whitney rank sum test).

See Tables 1 and 2 for remainder of key.

Overall, 23 of 32 (72%) cat owners characterized the treatment plan (considering all visits to the hospital and all drugs prescribed) as cost-effective; the proportion that selected this assessment did not differ (P = 0.115) between owners of cats in the low-dose (13/21 [62%]) or high-dose (10/11) famciclovir treatment groups. Of the 30 owners who subjectively ranked the effectiveness of the drugs for reducing signs of disease, 21 (70%) perceived famciclovir as the most effective (13/30 [43%]) or second most effective (8/30 [27%]) drug that was prescribed for their cat. Four owners reported adverse effects that they thought might have been attributable to the prescribed medications, including mydriasis and vomiting (1 cat each; both effects attributed to topically administered atropine) and signs of ocular irritation (2 cats; signs were attributed to topically applied ophthalmic tobramycin in 1 cat and to famciclovir administered PO in the other).

Discussion

In the present retrospective study, clinical improvement was evident in the medical records of 50 of 59 (85%) cats that received famciclovir PO 3 times/d at a low (approx 40 mg/kg) or high dose (approx 90 mg/kg), with or without other concurrent treatments, for presumed FHV-1 infection. Twenty-five of 32 (78%) cat owners reported that clinical signs were permanently or temporarily improved with the treatments used, and 21 of 30 (70%) cat owners perceived famciclovir as the most effective or second most effective drug for reducing clinical signs of disease in their pet.

Although median duration of clinical signs prior to initiation of famciclovir in the present study was approximately 40 days, it is important to note that 15 of 59 (25%) cats had clinical signs for ≥ 6 months prior to referral to the hospital where the study was performed. Despite the chronicity of clinical signs in many cats, most improved rapidly after initiation of the famciclovir treatment (median time to improvement, 13 days; range, 3 to 183 days). Furthermore, most (44/59 [75%]) cats required only 1 course of treatment with famciclovir during the present study, which was consistent with 17 of 32 (53%) owners surveyed rating their cat's improvement as permanent. Taken together, data from the medical records review and owner surveys strongly supported administration of famciclovir at doses ≥ 30 mg/kg, PO, 3 times/d for treatment of cats with signs of disease attributable to FHV-1 infection. The successful results in cats that received famciclovir in the present study were consistent with data from a previous efficacy study[12] in cats experimentally infected with FHV-1 and from a case series[16] of 10 client-owned cats.

In the present study, cats in the high-dose famciclovir treatment group had significantly greater clinical improvement (as assessed by retrospectively assigned disease severity scores), significantly shorter time to clinical improvement, and significantly shorter median duration of treatment than did cats in the low-dose group. Additionally, 11 of 11 owners of cats in the high-dose group who responded to our survey were classified as satisfied, and did not rate concerns over cost or ease of giving medications differently than did the 21 owners of cats in the low-dose group. Results of a previous study[13] by our group showed that similar maximum plasma concentrations and areas under the plasma concentration-versus-time curve for penciclovir were achieved in healthy cats receiving a single oral dose of 40 or 90 mg of famciclovir/kg, suggesting that the higher dose might not be necessary. In addition, a clinical case series report[16] found a positive effect of famciclovir treatment for cats with clinical signs attributed to FHV-1 infection, but the doses (and administration frequencies for some cats) were notably lower than those tested in the present study or experimentally.[12] Taken together, data from 3 previous studies[12,13,16] provided an impetus approximately halfway through the period covered by the present retrospective study for PO administration of famciclovir at a dosage of 40 mg/kg instead of 90 mg/kg 3 times/d in client-owned cats. Thus, it was surprising that data from this study showed that cats receiving approximately 90 mg of famciclovir/kg had better clinical outcomes than those that received the lower dose at the same frequency, and this confirms the complexity of famciclovir and penciclovir metabolism in cats. It is possible that the differences observed were attributable to other differences between the patient populations; however, ordered logistic regression showed that age, breed, sex, disease severity, duration of clinical signs, follow-up time, famciclovir treatment duration, number of courses of famciclovir treatment, and concurrent surgical intervention did not significantly affect the difference in clinical improvement seen between the 2 famciclovir dose groups. It is also possible that an alteration in drug formulation between the 2 dose groups contributed to the differences detected. For example, a greater proportion of cats in the high-dose group (15/18) received famciclovir from source A,[d] compared with cats in the low-dose group (2/16). However, it should be noted that the source of famciclovir could not be identified in 24 of 59 cats (41%) in the present study. Finally, it is possible that plasma concentrations, tear concentrations, or both are greater when famciclovir is administered PO at 90 versus 40 mg/kg 3 times/d. Recently, we found that penciclovir concentrations in tears were positively correlated with the famciclovir dose in client-owned cats administered 39 to 72 mg of famciclovir/kg, PO, 3 times/d.[15] A prospective, masked, placebo-controlled clinical trial of famciclovir with sufficient subjects comparing different dosages, different formulations, or both would be necessary to answer these questions. Data from the present study can be used to inform the power studies critical to such prospective assessments.

A major impetus for administration of a lower dose or less frequent dosing of famciclovir is the cost of this medication, although the cost of famciclovir to

our clients declined overall as this study progressed. However, most owners completing the survey ranked the degree of improvement in their cat's illness as having greater importance (median score, 10/10) than the cost of medications (median score, 8/10). Likewise, the importance owners placed on cost of treatment did not significantly differ between owners of cats in the low-dose and high-dose famciclovir treatment groups, and most (23/32 [72%]) owners characterized their cat's treatment plan, including all hospital visits and treatments prescribed, as cost-effective. This was particularly important, considering that owners of cats in the high-dose group were not only required to purchase approximately twice as much famciclovir as those in the low-dose group, but also likely to have paid more for a given amount of the drug than did owners of low-dose group cats because this dose was administered prior to the drug becoming available in generic form. It is also interesting to speculate on the combined effect of treatment dose and duration on cost and owner commitment. The median famciclovir dose for cats in the high-dose group was 2.1 times that given to the low-dose group, but it was associated with a median treatment duration and median time to improvement that were 22 days (61%) and 7 days (50%), respectively, shorter than those for cats receiving the low dose. Assuming a fixed cost of famciclovir and that the number of recheck examinations could also be reduced as treatment duration and time to improvement decrease, use of a higher dose of famciclovir could be associated with reduction in the overall cost for the client, although the number of recheck appointments did not differ between the 2 treatment groups in the present study. Overall cost to the client should be assessed in future prospective trials. Data regarding owner tolerance of cost in the present study must be interpreted in light of the fact that the facility where the study was performed is typically a secondary or tertiary referral center for patients with chronic, severe, or recurrent disease such as many of those included in the present study, and it is likely that these data were not representative of those that would be generated from owners whose cats are seen and treated by general practitioners. Regardless, it is important that veterinarians consider likely treatment duration and discuss overall treatment costs with owners rather than simply a cost per day or per dose.

In human patients infected with HSV-1, high-dose, patient-initiated episodic antiviral treatment has similar safety and efficacy to more traditional, longer treatment regimens.[20] Although results of 1 study[21] revealed that a single (125 or 500 mg) dose of famciclovir for the treatment of FHV-1 in shelter-housed cats did not limit disease, alternative antiviral treatment regimens such as episodic high-dose administration may have merit in FHV-1–infected client-owned cats; these treatment methods could produce further cost savings and warrant further investigation. Most (17/32 [53%]) cat owners responding to the survey in the present study rated their cat's improvement after treatment as permanent. Although this was a subjective assessment by unmasked observers and defined by the period between the completion of treatment and completion of the survey, the finding was intriguing. Considering that many of the cats had chronic signs of disease prior to treatment at the study facility, it is interesting to speculate on the mechanism by which famciclovir could have contributed or led to apparent resolution rather than remission of clinical signs. It is possible that some of these cats had disease resulting from chronically persistent virus within a peripheral tissue, rather than frequent reactivation of virus from neural reservoirs, as has been suggested for other herpesviruses,[22] and that this persistent virus was cleared by famciclovir.

Most cats (49/59 [83%]) in the present study had no evidence of adverse effects potentially attributed to famciclovir administration. Although many cats in the present study were treated with famciclovir for < 1 month, 8 cats received famciclovir for > 3 months, including 1 cat that received 100 mg/kg 3 times/d for 2.4 years, and none of these 8 cats experienced any adverse effects. Among the 10 cats with adverse effects potentially attributable to famciclovir, gastrointestinal signs were most common and included diarrhea (4/59 [7%]), anorexia (2 [3%]), vomiting (1 [2%]), and weight loss (1 [2%]). The nature, severity, and reversibility of these adverse effects were similar to those reported in humans receiving famciclovir for the treatment of disease attributed to herpes zoster virus infection.[23] In addition, 2 cats in the present study had polydipsia, and 1 of these had a concurrent reduction in USG. In this latter cat, polydipsia resolved after famciclovir treatment was discontinued, although the USG remained low, and the cat was diagnosed as having chronic renal disease (International Renal Interest Society system stage II) approximately 3 years after the treatment ended. Although we considered it likely that this cat had preexisting renal disease, this could not be verified and it is possible that famciclovir administration influenced the condition. We previously evaluated the safety of famciclovir in a total of 24 cats during several pharmacokinetic and efficacy studies.[11–13] Although the cats in those studies were young and healthy and the treatment courses were generally shorter than those described in the present clinical study, we did not identify any clinical signs or serum or urine biochemical changes suggestive of renal or other specific organ toxicosis in any cat. In contrast, administration of the pharmacologically related antiviral prodrug valacyclovir at 60 mg/kg (27.3 mg/lb), PO, every 6 hours to cats experimentally infected with FHV-1 resulted in coagulative necrosis of the renal tubular epithelium as well as centrilobular hepatic atrophy and severe bone marrow suppression.[10] Famciclovir and valacyclovir are prodrugs intended to promote bioavailability of the active metabolites penciclovir and acyclovir, respectively. In humans, famciclovir has been substituted for acyclo-

vir in patients with acyclovir-associated renal toxicosis secondary to crystallizing nephropathy.[24] The pharmacokinetics of famciclovir has been assessed in humans with renal compromise, and a decrease in dose frequency is recommended in this patient population.[25] Therefore, despite the low frequency of renal signs in patients of the present study and inability to establish causation, famciclovir should be used judiciously in feline patients with preexisting renal disease, perhaps at a decreased dose frequency as is recommended in humans, and renal variables and clinical signs should be closely monitored in such patients. Finally, because serum biochemical analysis, urinalysis, and hematologic investigations were not routinely conducted for patients in the present study, it is possible that some cats had clinicopathologic evidence of toxicosis that was insufficiently severe to produce clinically observable adverse effects. We also recognize that a prospective experimental study or clinical trial is necessary to rigorously assess for adverse effects of chronic (> 1 month) administration of oral famciclovir. However, considering all data, the results of the present study supported that famciclovir has a notably greater safety margin in cats, compared with that described for valacyclovir, which is the only other systemic antiviral prodrug drug evaluated in cats.

In the present study, 12 cats were < 7 months of age, and some were only 12 days old. To the authors' knowledge, this is the first report of juvenile cats being treated with famciclovir PO. Because the smallest commercially available famciclovir product is a 125 mg tablet, tablets for juvenile cats in this study weighing as little as 0.2 kg (0.44 lb) typically had to be split into eighths or sixteenths to approximate the 2 targeted doses in the present study. Despite these efforts, some of these patients received famciclovir doses as high as 140 mg/kg 3 times/d, although juvenile cats typically had a shorter duration of treatment (median of 8 days) than did the overall study population or geriatric cats (median of 24 days or 41 days, respectively). Following treatment with famciclovir, all 12 kittens had clinical improvement in 3 to 14 days, subjectively scored as marked in 10 and mild in 2. This finding, in combination with results of our previous study[12] in which FHV-1–naïve cats experimentally infected with FHV-1 had marked improvement following famciclovir treatment at 90 mg/kg, PO, 3 times/d, suggested that disease attributable to primary FHV-1 infection may be particularly amenable to treatment with famciclovir. Importantly, no juvenile cats in the present study had adverse effects detected. These results contrast with studies[26,27] of human infants and children receiving famciclovir, in which adverse effects, typically gastrointestinal in nature, occurred in up to 26 of 47 (55%) patients.

Famciclovir was also administered to 14 cats considered geriatric for the purposes of the present study (10 to 16 years of age). In 11 of 14 geriatric cats, clinical signs improved at 13 days following treatment with famciclovir PO, 3 times/d. These results are consistent with a previous study[16] that reported improved clinical signs following treatment with famciclovir in 3 cats > 10 years of age. However, 5 of 14 geriatric cats in the present study had adverse effects reported, including anorexia (n = 2), polydipsia with a concurrent decrease in USG (1), polydipsia with no change in USG (1), and increased hiding behavior attributed to pill administration by the owner (1). It was difficult to discern whether adverse effects were related to famciclovir administration, concurrent disease processes, or other concurrently administered treatments. Given that geriatric cats required a relatively long treatment period (median, 41 days) in the present study and are at increased risk for renal and other systemic diseases, compared with younger cats, it may be prudent to perform a CBC, serum biochemical analysis, and urinalysis prior to instituting famciclovir in aged cats. If adverse effects are detected, these tests can be repeated and the results compared with those performed prior to initiation of famciclovir.

Limitations of this study were typical of those commonly identified in retrospective studies. Improvement was rated by the attending clinicians and cat owners who were not masked to the treatment or famciclovir dose provided. A diagnosis of FHV-1 was not confirmed in most patients, as a laboratory assay that confirms the etiologic role of FHV-1 in any given disease process does not exist.[28–30] Furthermore, diagnostic testing for an etiologic cause of clinical signs was not pursued in most cats. Therefore, it remains possible that the clinical outcomes observed in the present study occurred as a result of or coincident with the therapies chosen, but that some or all signs were attributable to a cause other than FHV-1. Likewise, because this was a retrospective review of medical records, a placebo-treated control group was not available for comparison, famciclovir administration was started and stopped at the discretion of the treating clinicians in consultation with the owners, and owner compliance with the prescribed treatment was not critically assessed. Additionally, follow-up time was variable among cats, which made it difficult to evaluate whether improvement was permanent or temporary and could have influenced the time to improvement of clinical signs in some patients. Finally, it is possible that some cats had clinical improvement attributable at least in part to treatments other than famciclovir (although the median change in the number of other medications prescribed was 0, and many cats had chronic signs of disease prior to the study treatments) or as part of the natural course of herpetic disease. Despite these shortcomings, results of the present study indicated that famciclovir at the dosages prescribed was associated with improved clinical signs in feline patients with varying degrees of illness, including several with chronic disease attributed to FHV-1, and few adverse effects were attributed to the treatment. Prospective, masked, con-

trolled studies are needed to fully evaluate the efficacy and safety of famciclovir treatment in cats confirmed to have FHV-1 infection and to determine whether a famciclovir dosage of 90 versus 40 mg/kg, PO, 3 times/d would result in increased efficacy with a shorter and potentially more cost-effective treatment course in these patients.

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Footnotes

a. Graphpad QuickCalcs 2014. Available at: graphpad.com/quickcalcs/contingency1.cfm. Accessed Aug 14, 2014.
b. SigmaPlot, version 12.0, Systat Software Inc, San Jose, Calif.
c. Stata/IC, version 13.1, StataCorp LP, College Station, Tex.
d. Famvir, Novartis Pharma AG, Basel, Switzerland.
e. Famciclovir, TEVA Pharmaceuticals Industries Ltd, Petah Tikva, Israel.
f. Acell Vet Inc, Columbia, Md.

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